UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,844	11/16/2001	C. Frank Bennett	ISPH-0617	2097

26259 7590 01/22/2004

LICATLA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/001,844	BENNETT ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- Th MAILING DATE of this communication appears on the cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11/16/2001* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Pursuant to 35 U.S.C. 121 and 37 C.F.R. 1.141, the antisense sequences listed in claim 3 are subject to restriction. The Commissioner has partially waived the requirements of 37 C.F.R. 1.141 and will permit a reasonable number of such nucleotide sequences to be claimed in a single application. Under this policy, up to 10 of independent and distinct nucleotide sequences will be examined in a single application. (see MPEP 803.04 and 2434)

Claim 3 specifically claims antisense SEQ ID NOS: 15, 28, 29, 31-36, 38, 39, 41-43, and 45-49, which are targeted to and modulate the expression of Sonic hedgehog (SHH). Although the antisense sequences claimed each target and modulate expression of the same gene, the instant antisense sequences are considered to be unrelated, since each antisense sequence claimed is structurally and functionally independent and distinct for the following reasons: each antisense sequence has a unique nucleotide sequence, each antisense sequence targets a different and specific region of SHH, and each antisense, upon binding to SHH, functionally modulates (increases or decreases) the expression of the gene and to varying degree (per applicants' Table 1 in the specification). Furthermore, a search of more than one (1) of the antisense sequences claimed in claim 3 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed antisense sequences. In view of the foregoing, one (1) antisense sequence is considered to be a reasonable number of sequences for examination. Accordingly, applicants are required to elect one (1) antisense sequence from claim 3.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Response to Election/Restrictions

2. As a result of a telephone conversation with Jane Massey Licata regarding the restriction requirement above, applicants filed a preliminary amendment whereby claim 3, reciting antisense SEQ ID NOS: 15, 28, 29, 31-36, 38, 39, 41-43, and 45-49 was canceled, and claim 1 was amended to recite a single target sequence. This preliminary amendment is considered responsive to the restriction requirement above, because a single nucleotide sequence, i.e. the target sequence, has been elected, and claim 3 which recites the sequences necessitating the restriction requirement, has been canceled. Accordingly, applicants have elected to prosecute any antisense targeted to SEQ ID NO: 3. An action on the merits of this invention follows.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 2, 4-10, and 12-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "A compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding SHH (SEQ ID NO:3), wherein said compound specifically hybridizes with said nucleic acid molecule encoding SHH and inhibits the expression of SHH."

It is unclear if the reference to SEQ ID NO: 3 refers back to the SHH protein, or the nucleic acid molecule encoding SHH.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of Sonic hedgehog (SHH, SEQ ID NO: 3) expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of

SHH expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of SHH in cells or tissues comprising contacting said cells or tissues with antisense compositions that inhibit the expression of SHH, wherein the language of said claims encompasses both *in vivo* and *in vitro* activity. The claims of the above invention are also drawn to methods of treating an animal having a condition associated with SHH, wherein said compositions are administered to animals such that expression of SHH is inhibited, wherein said condition may be cancer, or a condition characterized by an insensitivity to apoptotic signals, or is an autoimmune or inflammatory disorder. The specification teaches a method of using the claimed compositions to inhibit the expression of SHH in cells *in vitro*.

The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in vitro* is unpredictable. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) review article by Braasch et al. concludes that major obstacles persist in the art of using antisense oligos in treating disease: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. specifically identify 3 factors that contribute to the unpredictable efficacy of using antisense compounds in general: 1) the variable capability of antisense oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the antisense oligos by cells, with the result that "the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death"; and 3), that "oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. elaborates, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal

structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target, and that "[a]ttempts to describe the *in vivo* structure of RNA, in contrast to DNA, have been fraught with difficulty." (Page 3161, second column).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states that "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379). Gewirtz adds that [t]he other major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient."

Branch et al. discuss the problems pertaining to non-specific oligo interactions that lead to artifactual phenotypes during *in vivo* antisense administration: "non-antisense effects are not

currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, regarding the therapeutic benefit of antisense technology in general, Branch states that "in fact, nucleic acid drugs should not be thought of as magic bullets. Their therapeutic use will require vigilant monitoring. Compared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs extend only across a narrow concentration range. Both *in vitro* and *in vivo*, less than a factor of ten often separates the concentration producing no antisense effect form that producing the full antisense effect. Steep dose-response curves commonly indicate that a drug has multiple, synergistic mechanisms of action. A drug with a narrow therapeutic window can be potent and extremely valuable, but can also be tricky to use safely. Since the ratio of antisense to non-antisense effects drops sharply outside a restricted concentration range, it will be challenging to obtain consistent therapeutic benefit (Page 46, second column).

Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

Finally, Branch states that "[i]t is not yet clear whether *in vitro* screening techniques of the sort used by Milner and co-workers will identify ODNs that are effective *in vivo*. With so

many possible sequences to choose from, and the likelihood that *in vitro* studies will not always predict *in vivo* efficacy, straightforward new screening techniques need to be developed for use in cells."

Thus, it is maintained that the prior art at the time of applicants' filing would not enable the use of *in vitro* antisense screening techniques to support claims directed to the *in vivo* use of antisense, let alone claims directed to therapeutic use *in vivo*. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification in the form of *in vitro* examples and broad prophetic treatment regimens enough to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

This is particularly true in view of the claimed breadth of claims 16-20, which pertain to treating or preventing any condition or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the antisense administered, and specifically regarding the instant compositions and methods claimed.

Since the specification fails to provide any real guidance for the methods of using antisense *in vivo* or in the successful treatment or prevention of such a broad range of diseases, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the

invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of those sequences that are successfully delivered to target sites in appropriate cells and /or tissues such that inhibition is achieved and treatment attained. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1, 2, 4, 5, 11, 12, 14, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Sadler et al. [Methods in Developmental Toxicology and Biology, (International Symposium on "Methods in Developmental Toxicology and Biology"), Berlin, May 31-June 2, 1995 (1997), Meeting Date 1995, 125-133. Editors: Klug, Stephan; Thiel, Renate. Blackwell: Oxford, UK].

The invention of the above claims is drawn to an antisense oligonucleotide 8 to 50 nucleobases long that specifically hybridizes to and inhibits the expression of SHH of SEQ ID NO: 3, wherein said oligonucleotide is modified, wherein said modification may be a phosphorothioate modification, or wherein said compound hybridizes to an active site on SHH, or wherein said compound is in a pharmaceutically acceptable carrier, and to a method for using said oligonucleotide comprising contacting said oligonucleotide in a cell so that expression of SHH is inhibited.

Sadler et al. teaches an antisense oligonucleotide that is 20 nucleobases long that is complementary to and inhibits SHH, wherein said oligonucleotide is phosphorothioated, and wherein said compound hybridizes to an active site on SHH, and wherein said compound is in a pharmaceutically acceptable carrier. Sadler et al. also teaches a method for using said oligonucleotide comprising contacting said oligonucleotide in a cell so that expression of SHH is inhibited.

9. Claims 1, 2, 4, 5, 11, 12, 14, and 15 rejected under 35 U.S.C. 102(e) as being anticipated by Ingham et al. (U. S. Patent Number 6,165,747).

The instant invention is drawn to the same invention as rejected under 35 U.S.C. § 102(b) above.

Ingham et al. teaches antisense oligonucleotides that are preferably 20 nucleobases long that are complementary to and inhibit the expression of SHH of SEQ ID NO: 3, wherein said oligonucleotides are phosphorothioated, and wherein said compounds hybridize to an active site on SHH, and wherein said compounds are in a pharmaceutically acceptable carrier. Ingham et al.

also teach a method for using said oligonucleotides comprising contacting said oligonucleotides in a cell so that expression of SHH is inhibited.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 2, and 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ingham or Sadler et al. in view of Taylor et al. (Drug Disc. Today, 1999. 4(12)562-567) and Barracchini et al. (U. S. Patent Number 5,801,154).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The invention of the above claims is drawn to antisense compounds that target SHH, or said compounds comprising internucleoside, nucleobase, and 2' modifications, chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents thereof.

Sadler et al. and Ingham et al. are relied upon as described above. Ingham additionally teaches applicants SEQ ID NO: 3. Neither Sadler et al. nor Ingham et al. teach modified oligonucleotides comprising nucleobase or 2' modifications or chimeras, or said oligonucleotides in a colloidal dispersion delivery system.

Taylor et al. teach the inhibition of expression of any protein using a known cDNA sequence to generate antisense oligos that target that and inhibit the expression of that protein, and also teach that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Baracchini et al. teaches modifications of antisense compounds comprising sugar, nucleobase, 2' modifications, chimeras, and compositions comprising said compounds and pharmaceutically acceptable diluents and dispersion systems thereof. Baracchini et al. also teach targeting specific regions of a gene including the 5'-untranslated, start codon, coding, stop codon, or 3'-untranslated regions, and demonstrate the methods necessary to achieve gene inhibition.

It would have been obvious to one of ordinary skill in the art to incorporate the oligonucleotide modifications of Baracchini et al. into the already modified antisense oligonucleotides targeting SHH of SEQ ID NO: 3 taught by Sadler et al. and Ingham et al. One would have been motivated to create such modified compounds because Sadler et al. and Ingham et al. expressly teach that their modified oligos containing phosphorothioate linkages are more resistant to degradation compared to unmodified oligos, and because Baracchini et al. teach a number of modifications in addition to phosphorothioate modifications, such as 2'-O-methoxyethyl, 5-methylcytosine and chimeric modifications, that serve to increase an antisense

compound's cellular uptake, target affinity and resistance to degradation. Therefore, one of ordinary skill would have been motivated to use other types of modifications that confer the same advantages of lengthened half-life and uptake, such as those taught by Baracchini et al. Finally, one would have a reasonable expectation of success given that Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and since Baracchini et al. teach all the steps necessary to make such modified antisense compounds including starting reagents, concentrations, and incubation times, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600